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Profound haemodilution during normothermic cardiopulmonary bypass influences neither gastrointestinal permeability nor cytokine release in coronary artery bypass graft surgery

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Background. Cardiopulmonary bypass (CPB) impairs intestinal barrier function and induces systemic inflammation after cardiac surgery. The objective of this study was to evaluate the effect of profound haemodilution (haematocrit 19–21%) during normothermic CPB on gastrointestinal permeability and cytokine release in comparison with a standard haemodilution (haematocrit 24–26%).

Methods. This was a prospective, controlled, randomized pilot trial of 60 patients without gastrointestinal disease undergoing normothermic CPB (35.5–36°C) for coronary artery bypass graft surgery. Gastrointestinal permeability was measured by the triple-sugar technique (sucrose, lactulose, and mannitol excretion in urine) before and after CPB. Interleukin (IL)-6, IL-10, and tumour necrosis factor alpha (TNFα) were quantified using enzyme-linked immunosorbent assays.

Results. Data from 59 patients (19–21% haematocrit, $n=28$; 24–26% haematocrit, $n=31$) were analysed. Data on gastrointestinal permeability were available for 47 patients (19–21% haematocrit, $n=23$; 24–26% haematocrit, $n=24$), blood samples for cytokine analysis from 59 patients. Mannitol excretion was normal before and after surgery without significant differences between the groups (after operation: 5.4% *vs* 2.9%, $P=0.193$). Lactulose and sucrose excretion was within a normal range before surgery and increased afterwards without differences between the groups. IL-6, IL-10, and TNFα were elevated after surgery, but there was no difference between the groups [IL-6 ($P=0.78$), IL-10 ($P=0.74$), and TNFα ($P=0.67$)].

Conclusions. Profound haemodilution during normothermic CPB brought about significant changes neither in intestinal permeability nor in cytokine release. It may be concluded that a haematocrit of 19–21% during normothermic CPB does not impair intestinal barrier function and cytokine response in patients without gastrointestinal comorbidity.

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The concept of haemodilution using crystalloid solutions to avoid transfusions for open heart surgery was introduced by Neptune and colleagues[1] in 1959 and was thought to improve blood flow to tissues and to facilitate venous return.[2] In contrast to this concept, low haematocrit levels during cardiac surgery are often regarded as a trigger for blood transfusions to prevent a decrease in oxygen transport induced by haemodilutional anaemia. Transfusions, however, carry the risk of enhancing the postoperative inflammatory response[3] and are associated

high-performance liquid chromatography with pulsed electrochemical detection [Dionex, Idstein, Germany; chromatography module, 250×40 mm; Carbopac™ PA-1 column (Dionex); eluent, 150 mmol sodium hydroxide; flow rate, 1 ml min⁻¹].

Sucrose serves as a marker of gastroduodenal permeability.[16] Intestinal absorption of lactulose, a disaccharide containing galactose and fructose, predominantly occurs through an intercellular pathway via tight junctions, whereas mannitol is mainly absorbed intracellularly. The urine concentration of lactulose correlates with the permeability of the intestine, whereas the urine concentration of mannitol correlates with the mucosal surface area. The lactulose/mannitol (*L/M*) ratio, which is also called the permeability index (PI), was calculated by dividing urinary lactulose elimination by mannitol elimination. This was done to eliminate the effect of intestinal and extraintestinal losses as the PI is considered a more robust marker of intestinal permeability.[17] Normal values of PI are <0.03%.

Cytokines

The concentrations of IL-6, IL-10, and TNFα were measured during and after surgery. Arterial blood was obtained at five different time points: before surgery after haemodilution, 30 min after start of CPB, and 1, 6, and 18 h after admission to the ICU. Blood was drawn in tubes filled with ethylene diamine tetraacetic acid (Fa. Sarstedt, Nümbrecht, Germany) and centrifuged (Hettich, Tuttlingen, Germany) at 3000 rpm for 10 min. The supernatant was stored at −80°C. An enzyme-linked immunosorbent assay (Quantikine, R&D Systems, Minneapolis, MN, USA) was used. The lower detection limit of the IL-6 assay was 0.70 pg ml⁻¹, of the IL-10 assay 3.9 pg ml⁻¹, and of TNFα 7.8 pg ml⁻¹. The intra- and inter-assay coefficient of variance of the assays used were: IL-6 1.6−4.2% and 3.3−6.4%, IL-10 1.7−5.0% and 5.9−7.5%, and TNFα 5.3−8.1% and 9.3−10.0%, respectively.

Statistical methods

Owing to the limited sample sizes and non-symmetrically distributed observations, we used non-parametric statistics. Results were expressed as median and inter-quartile range (IQR) in the case of continuous variables. For gastrointestinal permeability, results were expressed as a percentage of recovery of the ingested dose of the sugars and the corresponding 25th and 75th percentiles. Absolute and relative frequencies were used for categorical and dichotomous variables. The effect of haemodilution regarding gastrointestinal permeability and cytokine response was analysed using χ^2 and Fisher's exact test for categorical and dichotomous variables, respectively. In the case of continuous variables, we applied the Mann–Whitney U-test for inter-group analysis. For longitudinal data, a non-parametric multivariate analysis of variance (non-parametric

MANOVA), described by Brunner,[18] for repeated measurements and small sample sizes in two and three factorial designs was used. Multiple testing for differences between the groups in question was regarded as exploratory and was not adjusted for multiplicity.

As this study was designed as an exploratory investigation to assess length of ICU stay in cardiac surgery patients subjected to profound haemodilution during normothermic CPB, power calculation was not performed before the study because it was evident that a planned number of 60 patients would not reach sufficient power for this clinical endpoint. A *post hoc* power calculation revealed a power of 20% for this endpoint.

A two-tailed $P<0.05$ was considered statistically significant. Statistical analysis was carried out using the Software Package for Social Sciences, 11.0 SPSS® for Windows® (SPSS, Inc., Chicago, IL, USA).

Results

After institutional approval by the local ethics committee and preoperative written informed consent, 60 patients undergoing CABG were considered eligible for this randomized controlled clinical trial. One patient had to be excluded from analysis as the autologous blood showed multiple clots after CPB and could not be retransfused. Fifty-nine patients remained for statistical analysis. Data from the triple-sugar test were available from 47 patients (19−21% haematocrit, $n=23$; 24−26% haematocrit, $n=24$), since preoperative urine samples could not be obtained from 12 patients. Data on cytokine release were available from all 59 patients. Patient characteristics are presented in Table 1.

Gut permeability

Mannitol

Preoperative and postoperative measurements of mannitol excretion were within normal limits (normal: <27% of the administered sugar). Median urinary mannitol excretion did not differ between the groups before surgery. The median (IQR) in the 20% haematocrit group was 16.6% (11.5−24.1%), whereas that in the 25% haematocrit group was 15.5% (10.5−23.1%, $P=0.439$). After surgery, mannitol excretion was significantly reduced in both groups: 20% haematocrit 5.4% (2.7−6.7%, $P<0.001$) and 25% haematocrit 2.9% (1.5−7.0%, $P<0.001$). Postoperative mannitol excretion did not differ between study groups ($P=0.193$) (Fig. 1A).

Lactulose

Preoperative lactulose excretion (normal: <0.44% of the administered sugar concentration) was within a normal range in the haematocrit 20% group with a median of 0.35% (0.2−0.5%) and in the haematocrit 25% group at 0.4% (0.2−0.7%). After operation, urinary excretion of

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Table 1 Two study groups: patient characteristics, times, and temperature during surgery

Characteristics	20% haematocrit (n=28)		25% haematocrit (n=31)	
	Median	IQR	Median	IQR
Age (yr)	63.5	57.25–70.25	60	54–69
Gender (M/F)	28/0	—	27/4	—
Height (m)	1.75	1.71–1.79	1.76	1.72–1.80
Weight (kg)	89.5	80.5–100.75	90	80–100
Duration of anaesthesia (min)	315	295–341.25	300	290–320
Duration of surgery (min)	202.5	175–240	200	160–220
CPB time (min)	72.5	63–80.75	74	52–83
Cross-clamp time (min)	44.5	38.25–49	45	32–58
Infusion of crystalloids (ml)	1000	1000–2000	1000	1000–1500
Temperature during operation (°C)	35.8	35.7–36.1	35.7	35.4–36.0
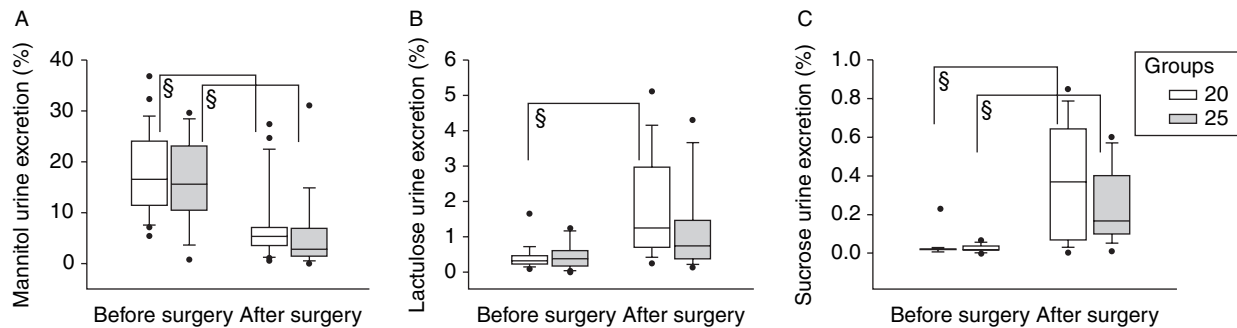
Fig 1 Triple-sugar test: urine excretion, before and after surgery. Results are given as box and whisker plots showing the median, IQR, and range. (A) *Mannitol*: the concentration was always within normal limits (<27%) and median values did not differ between the groups before surgery (P=0.439). After surgery, mannitol excretion was significantly reduced in both groups (§P<0.05), without significant differences between study groups: 20% haematocrit group 5.4% (2.7–6.7%) and 25% haematocrit group 2.9% (1.5–7.0%). (B) *Lactulose*: the urine excretion was within normal limits (<0.44%). After surgery, lactulose excretion was significantly increased in the 20% group (§P<0.05). There were no differences of lactulose excretion between the groups either before (P=0.940) or after surgery: 20% haematocrit group 1.2% (0.5–3.0%) and 25% haematocrit group 0.8% (0.3–1.4%). (C) *Sucrose*: after surgery, sucrose excretion was significantly increased in both groups (§P<0.05). The groups did not differ before surgery or after surgery: 20% haematocrit group 1.23% (0.4–3.2%) and 25% haematocrit group 0.65% (0.3–1.4%).

lactulose exceeded the normal range in both groups and was significantly increased compared with the baseline in the 20% haematocrit group with a median value of 1.2% (0.5–3.0%; P<0.001). The 25% haematocrit group showed a trend towards an increased permeability 0.8% (0.3–1.4%; P=0.073) after surgery. There were no differences in lactulose excretion between the groups (preoperative: P=0.940; postoperative: P=0.143) (Fig. 1B).

Sucrose
Sucrose excretion was elevated (normal: <0.23% of the administered sugar concentration) in both groups after surgery. The mean value in the haematocrit 20% group increased from 0.09% (25th–75th quartiles: 0.05–0.15%) to 1.23% (25th–75th quartiles: 0.4–3.2%) (P<0.001) and in the haematocrit 25% group from 0.12% (25th–75th quartiles: 0.00–0.22%) to 0.65% (25th–75th quartiles: 0.3–1.4%) (P<0.001). The groups did not differ before operation (P=0.776). After operation, an insignificant trend to a higher sucrose permeability (P=0.098) in the 20% haematocrit group was seen (Fig. 1C).

Permeability index
In both groups, the mean of PI was within the normal range before surgery without significant differences [20% haematocrit: 0.02 (0.02–0.02%); 25% haematocrit: 0.02% (0.02–0.09%)]. After surgery, an increase in lactulose and a decline in urinary mannitol excretion were measured in both groups. This resulted in a significant increase of the PI in both groups: in the 20% haematocrit group from 0.02 to 0.4 (0.07–0.7%, P<0.001) and in the 25% haematocrit group from 0.02 to 0.2 (0.09–0.4%, P<0.001) after surgery. The postoperative PI did not differ between the groups (before surgery: P=0.485; after surgery: P=0.288) (Fig. 2).

Perioperative cytokine release
IL-6 and IL-10
The time courses of IL-6 and IL-10 are shown in Figure 3A and B. The highest levels were reached 1 h after admission to the ICU and were for IL-6 121.2 pg ml^{-1} (108.7–178.7 pg ml^{-1}) in the 20% haematocrit group and 121.5 pg ml^{-1} (85.3–190.4 pg ml^{-1}) in the 25% haematocrit group (Fig. 3A). Highest levels of IL-10 in the 20%

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haematocrit group were 57.3 pg ml^{-1} (49.2–76.2 pg ml^{-1}) and in the 25% haematocrit group were 69.3 pg ml^{-1} (51.3–99.8 pg ml^{-1}). Levels declined continuously afterwards, yet never reached the initial values (Fig. 3B). In both groups, all measurements were significantly elevated compared with baseline values at all time points ($P<0.001$). There were no significant differences between the groups in the multivariate analysis of variance of Brunner ($P=0.78$ for IL-6; $P=0.74$ for IL-10).

Tumour necrosis factor alpha
The trend of TNFα plasma levels is shown in Fig. 4. Baseline values of TNFα (norm <15.6 pg ml^{-1}) did not differ between the groups; mean values in the 20% haematocrit group were 7.7 and 7.6 pg ml^{-1} in the 25% haematocrit group before surgery. Over the study period, TNFα

reached the highest levels in both groups 30 min after the start of CPB [20% haematocrit group 8.2 pg ml^{-1} (6.3–9.1 pg ml^{-1}) and 25% haematocrit group 8.3 pg ml^{-1} (7.5–9.3 pg ml^{-1})]. Thirty minutes after the start of CPB, TNFα plasma levels were significantly increased (20% haematocrit group: $P=0.03$; 25% haematocrit group: $P=0.008$) compared with the baseline. Between the groups, there were no differences over the study period ($P=0.67$) (Fig. 4).

Discussion

In our study, both intestinal surface and gastrointestinal barrier function were severely disturbed by normothermic CPB for elective CABG. We identified an increased release of cytokines (IL-6, IL-10, and TNFα) after surgery. However, profound haemodilution (haematocrit of 19–21%) *vs* standard haemodilution (haematocrit of 24–26%) did not have an impact on either intestinal barrier or inflammatory reactions.

Gastrointestinal permeability
Our results show that gastrointestinal permeability measured using a triple-sugar technique is increased after CPB; however, no differences were observed between profound and standard haemodilution.

Gastrointestinal permeability was evaluated indirectly by measurement of sugars in the urine. Sucrose and lactulose were elevated in postoperative urine samples which indicate an increased gastroduodenal and intestinal permeability, as these sugars are excreted only in very small amounts with the urine under physiological conditions. Moreover, the increase in intestinal permeability is confirmed by the increase in the PI, calculated as the ratio of
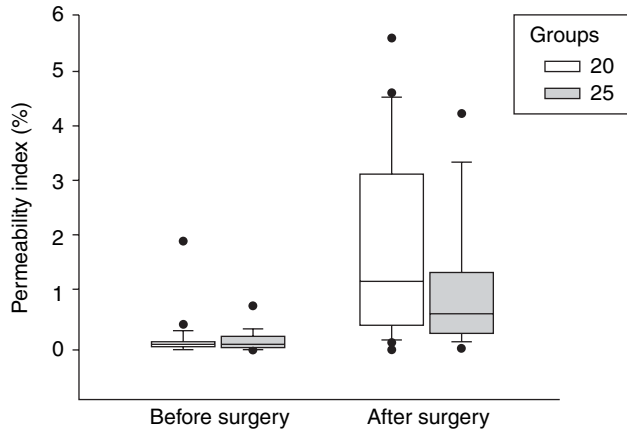
Fig 2 PI before and after surgery. The PI was calculated by dividing urinary lactulose excretion by mannitol excretion (reference range: lactulose %/mannitol %: <0.03%). The postoperative PI was not different between the groups either before surgery or after surgery.
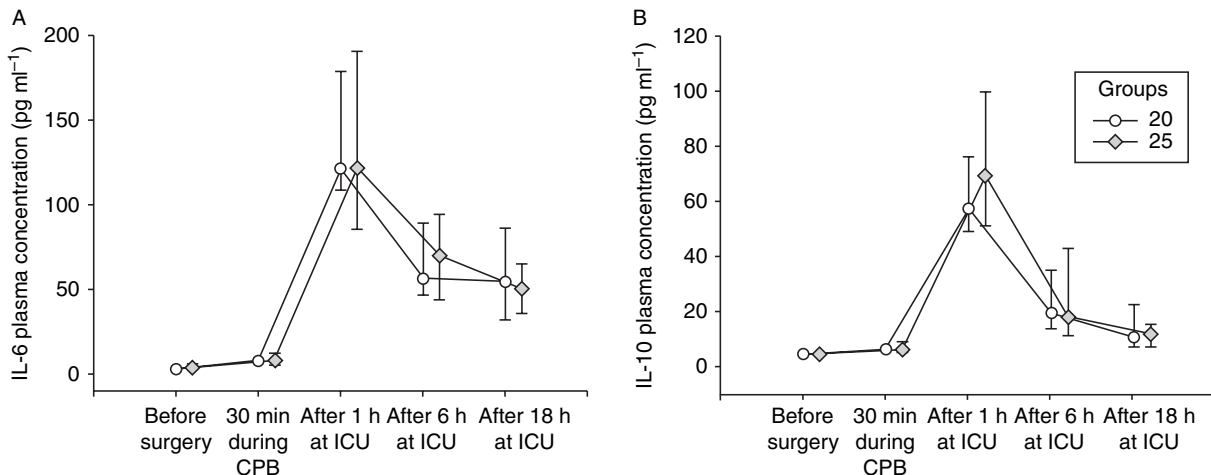
Fig 3 IL-6/IL-10 plasma concentrations. Results are given as median and range. Measurements took place before and 30 min during surgery and at ICU after 1, 6, and 18 h. (A) IL-6 (pg ml^{-1}) showed low levels before surgery, reached the peak 1 h after surgery at the ICU and declined within the first 6 h after surgery. There was no difference between the study groups ($P=0.78$). (B) IL-10 (pg ml^{-1}) showed highest plasma concentration 1 h after surgery and declined continuously afterwards, but never reached the initial values. There was no difference between the study groups.
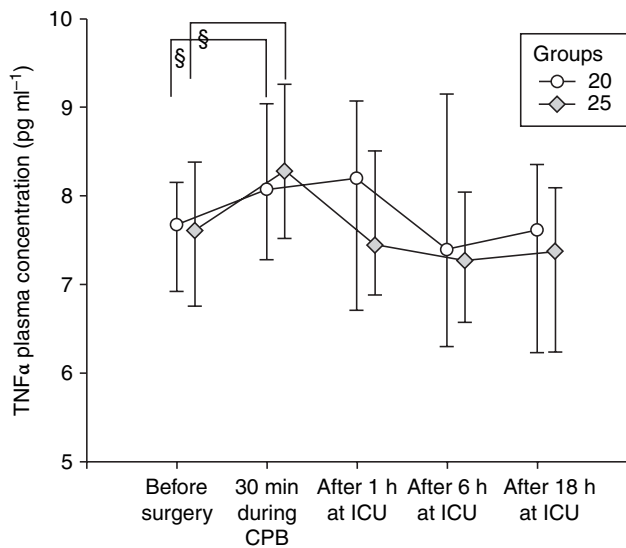
Fig 4 Baseline values of TNFα plasma concentration. Results are given as median and range. TNFα plasma concentration was measured at five measure points, before surgery, and 30 min during, after 1, 6, and 18 h at ICU. Over the study period, TNFα reached the highest levels in both groups 30 min after start of CPB [haematocrit 20% group: 8.20 pg ml^{-1} (25th−75th quartiles: 6.27−9.08 pg ml^{-1}); haematocrit 25% group: 8.29 pg ml^{-1} (25th−75th quartiles: 7.53−9.27 pg ml^{-1})]. Only at 30 min after start of CPB, TNFα plasma levels were significantly increased (§20% $P=0.03$ and §25% $P=0.008$) compared with baseline. Between the groups, there were no differences over the study period ($P=0.67$).

lactulose and mannitol excretion. The decline in mannitol excretion with the urine may reflect a decrease in mucosal surface induced by CPB. This is consistent with previous studies using this technique.[15] Although various studies have described an elevated gastrointestinal permeability after cardiac surgery,[19] the underlying cause for the observed increase in gastrointestinal permeability and its consequences for the patient are still unclear. It may be argued that haemodilutional anaemia is associated with a reduction in intestinal oxygen delivery and may impair mucosal integrity of the intestine. In eight patients with a haematocrit of 25−33% during CPB, Thoren and colleagues[19] observed increased perfusion of the jejunal mucosa, vasomotor activation of intestinal arterioles, and an elevated erythrocyte velocity and the jejunal mucosal haematocrit to be constant, despite systemic haemodilution. Those results were obtained under moderate hypothermia (34°C during CPB). Kleen and colleagues[20] described in anaesthetized dogs that profound normovolaemic haemodilution (haematocrit 19−21%) was accompanied by an elevated mucosal blood flow compared with a baseline haematocrit of 37 (3%). This group also showed in 16 splenectomized beagles that under profound haemodilution (haematocrit 19−21%), intestinal oxygen delivery did not decrease. It has to be emphasized, however, that temperature management during CPB was not controlled, so that possible differences in body temperatures may have influenced the results.[21]

The increase in intestinal permeability in our study may be explained by a reduction in intestinal oxygen delivery or loss of functional mucosal surface, which leads to a reduced absorption of mannitol. Previous work described that splanchnic oxygen consumption and arterial lactate concentrations were increased while splanchnic blood flow and oxygen delivery were not decreased during and after normothermic CPB.[7] This is in part supported by results from our own group showing that a haematocrit of 20% maintained global oxygen delivery above a critical level after elective CABG in low-risk patients.[13] Assuming a constant splanchnic blood flow,[14] our results may indicate that profound normovolaemic haemodilution under normothermia during CPB is still above a 'critical' level and is not a risk factor *per se* for increased intestinal permeability.

Cytokine release

Release of IL-6, IL-10, and TNFα did not differ between patients subjected to profound or standard haemodilution during normothermic CPB. The highest levels of IL-6 were measured 1 h after admission to the ICU in both groups which confirms results from other studies describing highest levels up to 3 h after surgery.[12 22] The relatively delayed increase in IL-6 might be explained by a 'reperfusion syndrome' after CPB.[23] Wan and colleagues[24] suggested that the post-ischaemic reperfusion of the myocardium is the source of IL-6 and TNFα. In their study, IL-10 reached its peak, similar to IL-6, 1 h after admission to the ICU and declined afterwards.[25]

In our study, TNFα levels did not show significant differences between the groups. This finding is supported by other studies.[26 27]

Aprotinin, which was used as routine antifibrinolytic therapy in our study, has been suggested to have immune modulating side-effects.[28] However, these were not confirmed by a randomized study of 200 patients undergoing CPB, in which neither the administration of aprotinin (2×10^6 U) nor of heparin (300 IU kg^{-1}) attenuated the release of TNFα, IL-6, and IL-8.[27] Given the fact that all patients underwent the same treatment, these immune modulating effects would have had to be similar in both groups. Furthermore, body temperature and the surgical trauma itself influence cytokine release after cardiac surgery.[29] In our study, these factors were evaluated and did not differ between the groups. Yet they may have contributed to the increase in cytokine levels. Although Naresh and colleagues[25] showed that IL-6 release, in contrast to TNFα, is temperature-dependent, our data indicate that profound haemodilution during normothermic CPB does not impair postoperative immune response.

In conclusion, the results of our trial showed that profound haemodilutional anaemia during normothermic CPB did not induce an increase in intestinal permeability or cytokine release compared with a standard haematocrit of

24–26%. It may be concluded that a haematocrit of 19–21% is safe to maintain the integrity of the intestinal mucosa and an adequate immune response in CABG patients subjected to normothermic CPB without gastrointestinal comorbidity. Since this study was designed as a pilot study, our results have to be confirmed by a larger and sufficiently powered study.

Funding

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